II. REMARKS

A. Status of the Claims:

Claims 5-18 and 21-25 were pending in this application. Claims 11 and 15-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b). Applicants, however, have expressly reserved the right to prosecute the non-elected claims in one or more continuing or divisional applications.

Claims 5-10, 12-14 and 21-25 have been examined and rejected on two grounds. The rejections are addressed in detail below. By virtue of this amendment, claims 5 and 21 have been amended to specify that the amount of lactoferrin administered must reduce the Langerhans cell migration or accumulation of dendritic cells in lymph nodes as a result of inflammation. The recitation of this limitation is supported by the language of claim 21 as previously presented, as well as the experimental results detailed in Examples 2 and 4. No new matter is added.

The specification at page 3 line 26 and page 38 line 24 has been amended to correct typographic errors. An issue of new matter is not raised by these amendments; entry thereof is respectfully requested.

B. Claim Rejections:

Under 35 U.S.C. § 102

Claims 5-7, 9, 12-14 and 21-25 stand rejected under 35 U. S. C. § 102 (e) as allegedly being anticipated by Conneely *et al.* (U. S. Patent 6,111,081). The rejection is overcome by the claim amendments specifying the amount of lactoferrin that must be used to treat an allergen-induced inflammation. The cited patent does not describe, expressly or inherently, the use of an amount of lactoferrin sufficient to reduce Langerhans cell migration or dendritic cell

accumulation in lymph nodes in response to inflammation. In fact, the cited patent does not even suggest that lactoferrin inhibits Langerhans cell migration or accumulation of dendritic cells in lymph nodes. Because the cited patent fails to describe each and every element of the amended claims, withdrawal of the rejection under 35 U. S. C. 102 (e) is respectfully requested.

Rejection under 35 U.S.C. § 103

(a) Conneely *et al.* (U. S. Patent 6,111,081):

Claims 5-10, 12-14 and 21-25 stand rejected under 35 U. S. C. §103 as allegedly being unpatentable over Conneely *et al.* (U. S. Patent 6,111,081). This rejection is overcome in light of the claim amendments for the reason statement above.

Moreover, effective November 29, 1999, this alleged prior patent under §103 via 35 U.S.C. §102 (e) is now disqualified as prior art against the claimed invention because the claimed invention were, at the time of the invention was made, owned by the same person or subject to obligation of the assignment to the same person. The instant application is a Continued Prosecution Application filed under 37 CFR 1.53(d) on April 9, 2001. Applicants hereby submit a copy of the Assignment in the priority application that establishes the common ownership. This rejection is thus moot.

(b) Teng *et al.* in combination of Britigan *et al.*, Greff, and De Lacharriere *et al.* (US Patent 5,658,581):

Claims 5-10, 12-14 and 20 stand rejected under 35 U. S. C. §103 (a) as allegedly being unpatentable over the primary reference Teng *et al.* in combination of the above-listed references. The Examiner states that Teng *et al.* teaches a method of treating human dermal

inflammatory disorder by administering a pharmaceutically effective amount of lactoferrin product, citing the disclosure at page 4, lines 21-30 of Teng *et al.*

Applicants have carefully reviewed the cited disclosure and respectfully disagree with the Examiner's characterization of Teng's teaching. The cited disclosure reads:

> "Another embodiment of the present invention relates to a method of treating a condition in a patient characterized by a deficiency in lactoferrin by administering to the patent an amount of human lactoferrin according to the present invention in sufficient quantities to eliminate the deficiency. The conditions include neutropenia, AIDS, skin infection, gastrointestinal bacterial overgrowth syndrome, vaginal infection and septic shock." Page 4, lines 21-30 of Teng *et al.*

A fair characterization of the cited disclosure would suggest that Teng teaches treating disorders as a result of lactoferrin deficiency and suggests restore the normal lactoferrin level in a subject. Teng does not teach treating any disorders unrelated to lactoferrin deficiency, such as disorders inflicted by exogenous substances, e.g. allergens. By contrast, the instant application teaches inhibition of allergen-inflicted inflammatory response by administering a therapeutically effective dose of lactoferrin, which certainly exceeds the normal level of lactoferrin *in vivo* (see the Example section of the specification). Following Teng's method to simply ameliorate the lactoferrin deficiency, one skilled in the art would not be able to treat the particular type of disorder as instantly claimed. This is particularly true in light of the claim amendments that require the use of an amount of lactoferrin sufficient to reduce Langerhans cell migration or dendritic cell accumulation in lymph nodes. Therefore, Teng's teaching cannot be relied on in any valid comparison with the present invention.

Additionally, it is inappropriate to equate skin infection caused by lactoferrin deficiency to dermal inflammation inflicted by an allergen. First, there is no indication of lack of lactoferrin in patients suffering from allergen-induced dermal inflammation. Second, there is a spectrum of

skin infections: some do not involve inflammation, and many are not related to allergen at all. To draw any inference from Teng *et al.* that the "skin infection" due to a lactoferrin deficiency is caused by an allergen and results in inflammation, is highly speculative and finds no basis in the cited disclosure.

Applicants further note that Teng *et al.* does not providing an enabling disclosure even for the limited suggestion of treating lactoferrin-deficient disorders, and thus does not qualify as prior art under section 103. As noted by the Court in Beckman Instruments Inc. v. LKB Produkter AB, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989): "[I]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the same apparatus or method." Teng *et al.* fails to teach how to determine or ascertain lactoferrin deficiency in a subject, how to replenish lactoferrin *in vivo*, and how to determine the *in vivo* efficacy of lactoferrin in treating the listed deficiencies. Absent these teachings, one skilled in the art is left with unlimited experimentation in attempt to devise a therapeutic scheme to correct lactoferrin deficiency (which is distinguished from the claimed invention) as Teng *et al.* have hoped to achieve.

Indeed, it was not reported until the present invention that lactoferrin binds to dermal cells such as keratinocytes, and inhibits cytokine production from these cells when inflicted by an allergen. It was also not shown or suggested until the present invention that lactoferrin exhibits anti allergen-induced inflammatory activity *in vivo* (e.g. in a mammal). Moreover, it was not described or even suggested by the cited art that lactoferrin can reduce inflammation-induced Langerhans cell migration and/or dendritic cell accumulation in lymph nodes; nor was there any suggestion as to how to determine the amount of lactoferrin required to yield such a therapeutic effect.

In summary, the Teng reference does not disclose or suggest any of the major elements of the present claims. It does not relate to the use of lactoferrin to treat allergen-induced disorders; nor does it suggest the use of an amount of lactoferrin that will be sufficient to reduce inflammation-induced dendritic cell accumulation in lymph nodes.

Turning now to the secondary references, Britigan *et al.*, Greff, and De Lacharriere *et al.* allegedly compensate the deficiencies in the teachings of the primary reference Teng *et al.* Britigan is cited for describing that lactoferrin has anti-inflammatory activity *in vitro*. However, Britigan does not adequately suggest that lactoferrin is a therapeutic agent for *in vivo* use; nor does it suggest that lactoferrin is a therapeutic agent for treating allergen-induced inflammation as instantly claimed. The only disclosure in Britigan is a general statement in the conclusion section that lactoferrin has the "*potential as a therapeutic agent*"; such potential is suggested as being "*worthy of continued study.*" At best Britigan provides the suggestion to try to test lactoferrin's *in vivo* use. Such suggestion falls short of the standard of a *prima facie* case of obviousness.

De Lacharriere *et al.* is cited for teaching the use of TNF α antagonists in pharmaceutical compositions. Nowhere in De Lacharriere describes that lactoferrin is a TNF antagonist. In fact the term "TNF α antagonists" is defined purely in functional terms, see column 3 lines 4-10 of the De Lacharriere patent. It is stated that "*all substances capable of inhibiting the release and/or synthesis and/or receptor binding of ...TNF alpha*" are considered "TNF α antagonists." Without teaching the structures of potential TNF α antagonists, no one in the art would know how to select a candidate from millions of natural and recombinant biological molecules in order to test for its ability to inhibit TNF α

production. Such a general statement in De Lacharriere cannot be fairly construed as providing a suggestion for one skilled in the art to select lactoferrin, and specifically, to test its ability to inhibit TNF α production in dermal cells, and to conduct the test under the particular condition that the mammal has been inflicted with an allergen.

Greff is cited in the present rejection as disclosing the use of lactoferrin for delaying skin aging, soothing inflammation, including UV-induced inflammation. Applicants respectfully disagree with the Examiner's characterization. The cited description is an abstract containing the following three sentences:

> "A cosmetic contains lactoferrins (I) as free radical scavengers, I may be present in liposome encapsulated formulations. The compn. furthermore contains antioxidants. The cosmetic is useful for the delay of aging of the skin and for soothing inflammation and solar erythema."

The disclosure suggests at best that the cosmetic is useful for delaying skin aging, soothing inflammation and solar erythema. It cannot be fairly read as suggesting that lactoferrin has the intended utility as the cosmetic contains other active ingredients such as antioxidants.

Even assuming that the reference remotely suggested the claimed method, Applicants find no disclosure or suggestion as to how one would use lactoferrin to treat allergen-induced inflammation in mammal; e.g., how to determine the *in vivo* efficacy of lactoferrin in treating the claimed disorders. There is absolutely no suggestion as to the amount of lactoferrin that must be used to effect the therapeutic utility, i.e. the amount of lactoferrin administered must be sufficient to reduce Langerhans cell migration or dendritic cell accumulation in lymph nodes. In fact, there is no suggestion in any of the references that lactoferrin reduces Langerhans cell migration or accumulation dendritic cells in lymph nodes. In view of the foregoing, Applicants respectfully

submit that the primary and secondary references do not suggest or in any way enable the specific methods of the present invention. Withdrawal of this rejection is respectfully requested.

(c) Teng *et al.* in combination of Nuijens *et al.*, and Enk et al, Database WPI AN 95-340208, and Penco et al:

Claims 5-10, 12-14 and 20 stand rejected under 35 U. S. C. §103 (a) as allegedly being unpatentable over the primary reference Teng *et al.* in combination of the above-listed references, all of which are of record.

As explained in the section above, the primary reference fails to describe the major elements of the present claims. There is no mention in Teng that lactoferrin can be used for treating disorders unrelated to lactoferrin deficiency in a subject. Moreover, Teng lacks suggestion for treating allergen-induced inflammation. In addition, the specific dose of lactoferrin and its ability to inhibit Langerhans cell migration or dendritic cell accumulation in response to local inflammation are not taught in Teng. As detailed below, these major elements of the present invention are not described or suggested in any one of the secondary references.

Nuijens *et al.* reports that lactoferrin suppresses IL-1 and TNF-α release from monocytes in response to LPS from Gram-negative bacteria. See last paragraph at page 287 that is cited by the Examiner. Nowhere in Nuijens teaches or suggests that lactoferrin suppresses IL-1 or TNF-α production from dermal cells in response to an allergen, which is mediated through an LPS independent pathway. As such, Nuijens *et al.* is not on point and adds nothing to the notion of using lactoferrin for treatment of dermal inflammation, and more specifically allergen-induced dermal inflammation.

Similarly, AN 95-340208 teaches the preparation and use of a lactoferrin composition that confers antimicrobial activity, which again relates to LPS pathway as stated and

distinguished in the specification. As such, AN 95-340208 fails to appreciate the anti-allergen activity of lactoferrin and fails to describe other required elements of the invention.

Enk *et al.* and Penco *et al.* report *in vitro* studies on two cytokines, namely IL-1β and TNF-α. Neither reference fairly suggests the relevance, if any, of the *in vitro* test to an *in vivo* application of lactoferrin.

When the cited secondary references are considered as a whole, Applicants find no suggestion for using the specified amount of lactoferrin for treating a specific condition that is unrelated to lactoferrin-deficient disorders. Given the extremely vague and general disclosure of the cited references, the references alone or in any combination, do not render the claimed methods obvious. Applicants request the Examiner reconsider and withdraw the rejection of the claims under §103.

III. CONCLUSION

Applicants respectfully submit that the above amendments and remarks fully respond to the rejection made in the Office Action mailed June 6, 2001. Applicants submit that the claims as amended are in allowable form and condition. The Examiner is invited to call the undersigned at (650) 463-8100 with any questions, comments or suggestions relating to this application.

Applicants hereby authorize the Commissioner to deduct any required fees from the Howrey Simon Arnold & White Deposit Account No. 08-3038, referencing docket no. 00138.0041.00US01.

Should any additional or fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is also authorized to deduct said fees from the same account.

Respectfully submitted,

Dated: December 5, 2001

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Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning at page 3 line 26 has been replaced with the following paragraph:

--One aspect of the present invention features compositions suppressing local inflammatory reactions. The compositions ~~comprises~~ comprise a lactoferrin and a pharmaceutically ~~accepta,ble~~ acceptable carrier. These compositions may alternatively, or in addition, include functional analogs or functional fragments of lactoferrin which exhibit the desired inhibitory activities on the locally induced TNF-α-dependent inflammation.--

The paragraph beginning at page 38 line 24 has been replaced with the following paragraph:

--Figure 5 shows the inhibitory effect of lactoferrin on oxazolone induced dendritic cell accumulation in draining lymph nodes when ~~lactoferrin~~ lactoferrin is applied topically to the skin surface.--

In the Claims:

Claims 5 and 21 have been amended as follows:

5. (Twice Amended) A method of treating an allergen-induced inflammatory disorder in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of a lactoferrin product, said amount being sufficient to reduce inflammation-induced Langerhans cell migration or accumulation of dendritic cells in lymph nodes.

21. (Amended) A method of inhibiting in a mammal a dermal inflammatory response ~~that is characterized by accumulation of dendritic cells in lymph nodes,~~ comprising administering to the mammal a ~~pharmaceutically~~ therapeutically effective amount of lactoferrin product, said amount being sufficient to ~~that reduces~~ reduce inflammation-induced ~~the~~ Langerhans cell migration or accumulation of dendritic cells in ~~the~~ lymph nodes.